19th Electronic Conference on Synthetic Organic Chemistry 2015

Synthesis of 6-triazolylmethyl-pyrrolo [3,4-*b*] pyridine-5-ones by an efficient MW- assisted (Ugi-3CR / aza Diels-Alder) / Click process.

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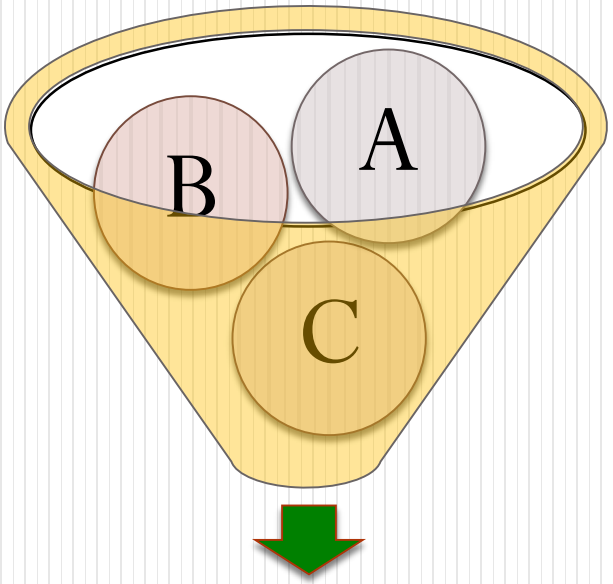
Universidad de Guanajuato, Mexíco.

Definition of Multi-component Reaction

Reactions in which more than two starting compounds react to form a product in such a way that the majority of the atoms of the starting material can be found in the product are called multi-component reactions.



Angew. Chem. Int. Ed. 2000, 39, 3268

History of MCRs

Non-Isocyanide based MCRs

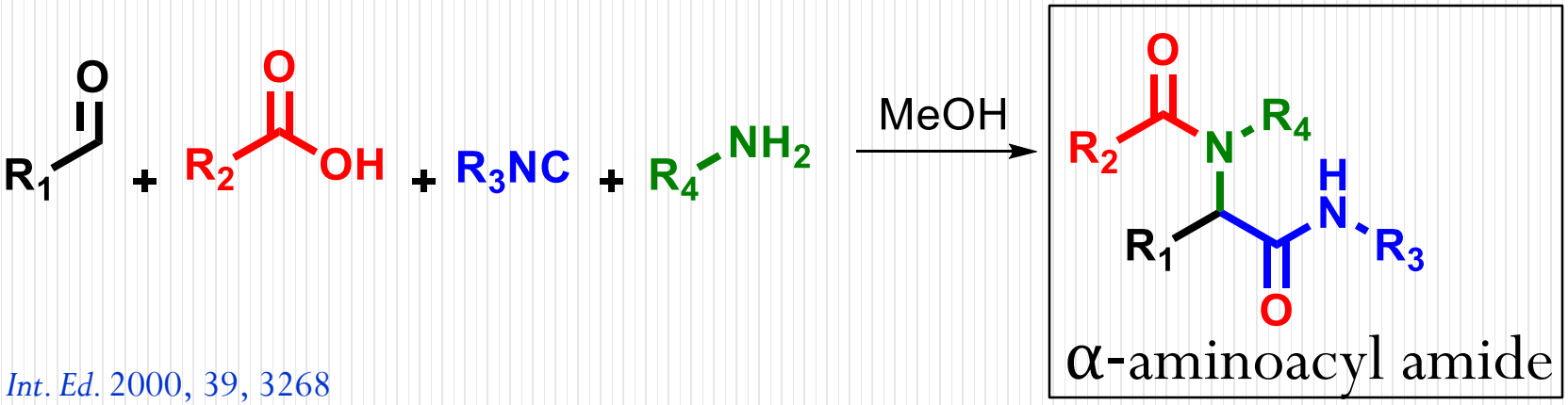
1838 – **Laurent and Gerhardt** – serendipitous MCR

1850 – **Strecker** synthesis of α-amino acids

Isocyanide based MCRs

1921 – **Mario Passerini** developed the first MCR involving isocyanides

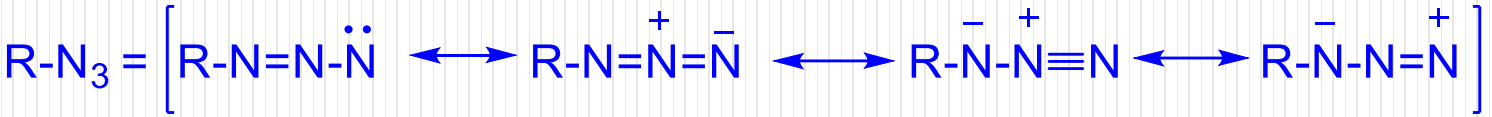
1959 – **Ivar Ugi** developed one of the most important and most studied MCRs involving isocyanides, having 4 components.



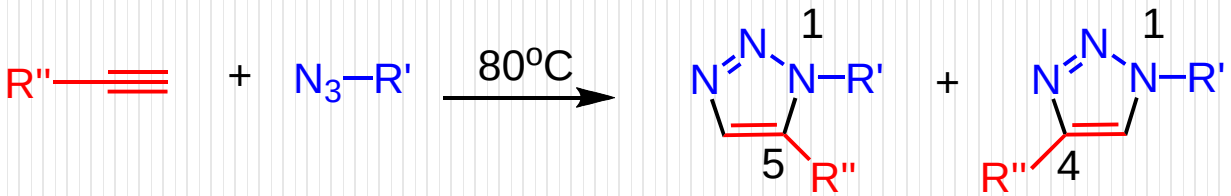
Angew. Chem. Int. Ed. 2000, 39, 3268

History of Azide/Alkyne Cycloadditions

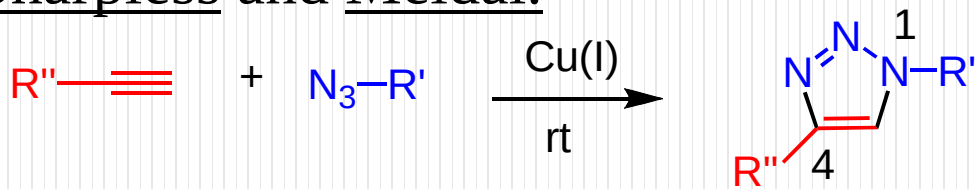
1933- Dipolar nature of azide was first recognized by Linus Pauling.



1960- Mechanism of 1,3-dipolar cycloaddition of azides- alkynes pioneered by Rolf Huisgen.

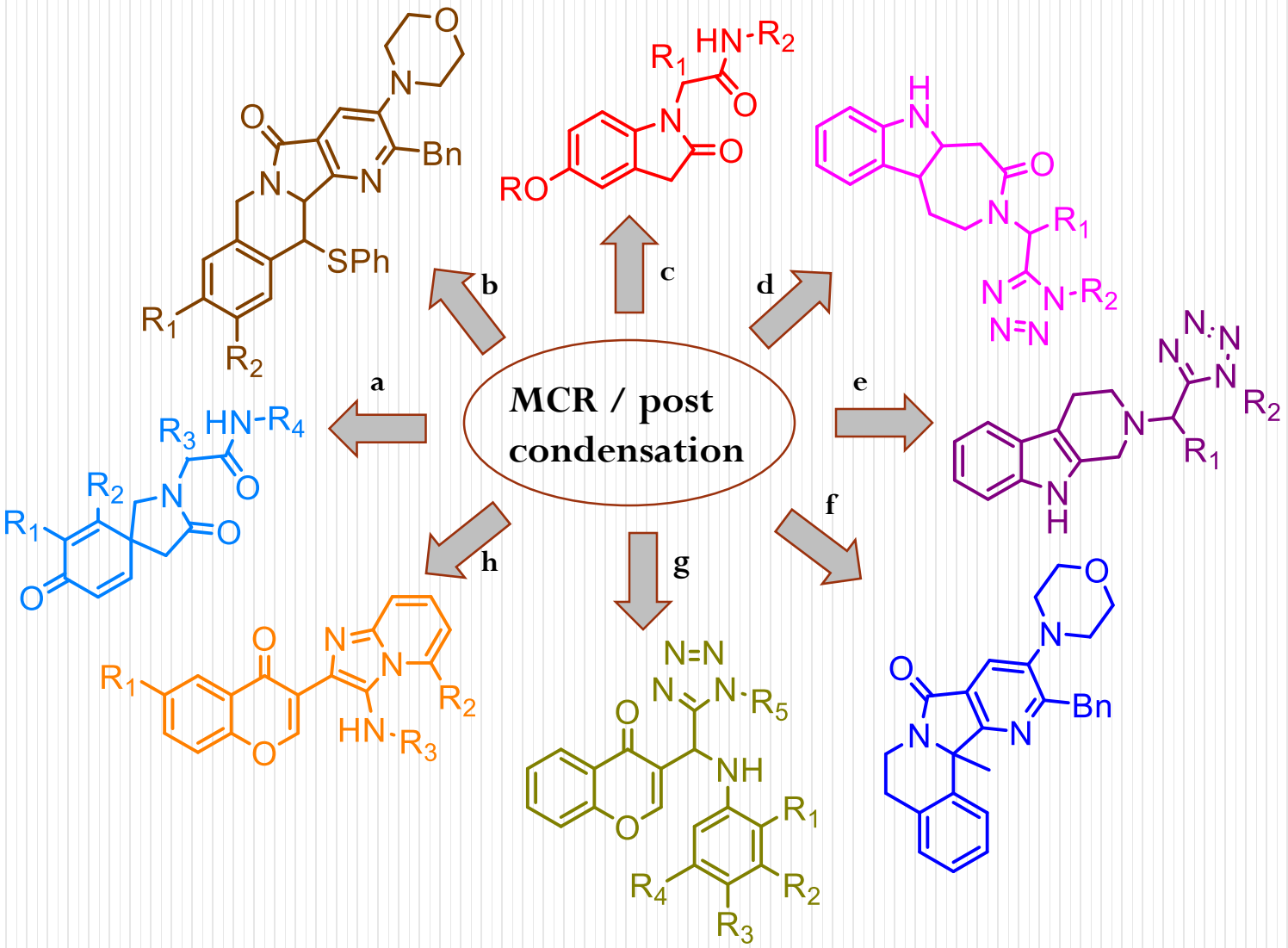


2001- Copper catalyzed 1,3-Dipolar azide-alkyne cycloaddition by Sharpless and Meldal.



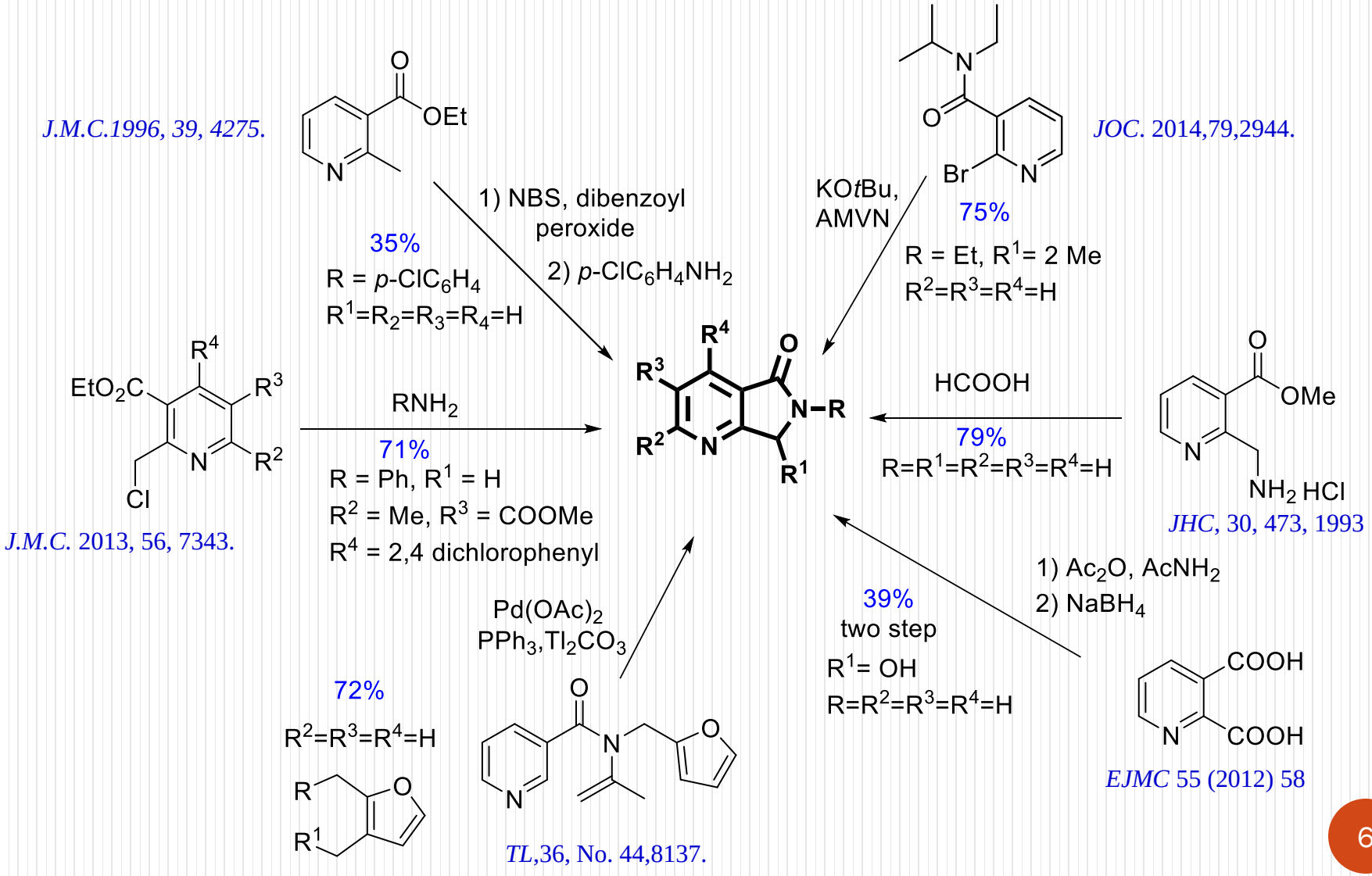
Angew. Chem. Int. Ed. 1963, 2, 633-66, Angew. Chem. Int. Ed. 2005, 44, 5188.

Our group work

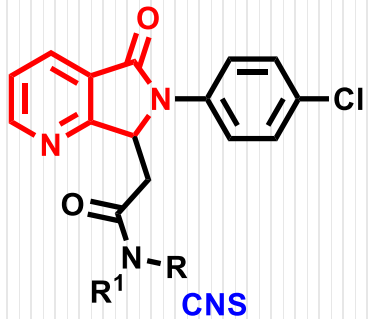


(a) *Synthesis*, **2010**, *8*, 1285; (b) *Tetrahedron Lett.* **2011**, *52*, 5245; (c) *Synlett* **2012**, *23*, 2951; (d) *Org. Biomol. Chem.* **2013**, *38*, 6470; (e) *Synthesis* **2014**, *46*, 49. (f) *Tetrahedron Lett, 2014,* 55, 6567. (g) Bioorg. Med. Chem. 2014, 22, 1370. (h) Tetrahedron Lett. 2015, 56,155.

Classical methods for the synthesis of Pyrrolo[3,4-*b*]pyridin-5-one derivatives

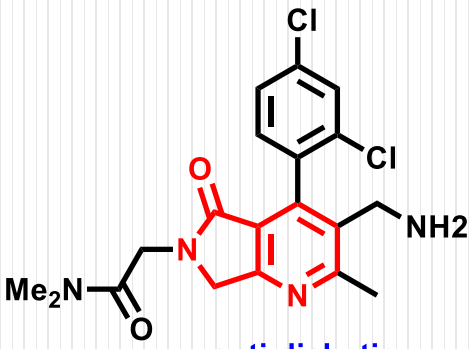


Medicinal applications of pyrrolo-pyridine, 1,2,3-triazoles and N H-1,2,3-triazoles.



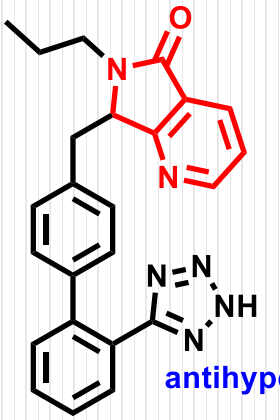
CNS

J. Med. Chem. 1996, 39, 4275.



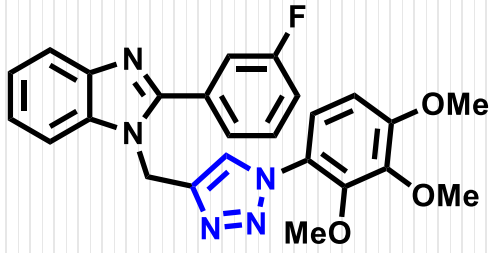
anti diabetic agent

J. Med. Chem. 2013, 56, 7343



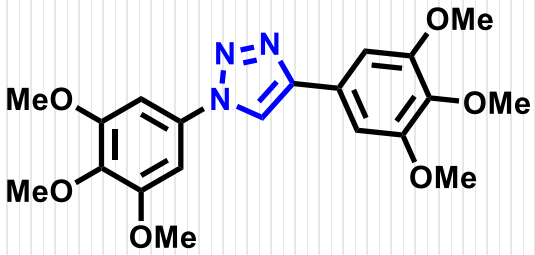
antihypertensive

J. Med. Chem. 2008, 51, 2137

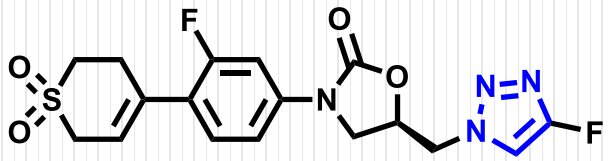


anti TB

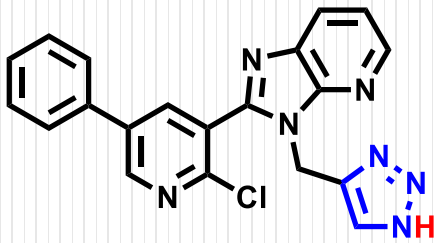
Chem. Asian J. 2011, 6, 2696



anti cancer

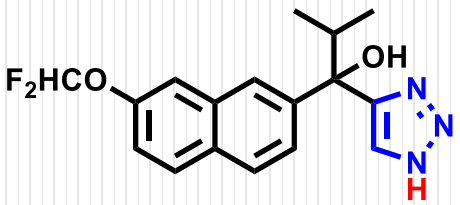


anti bacterial



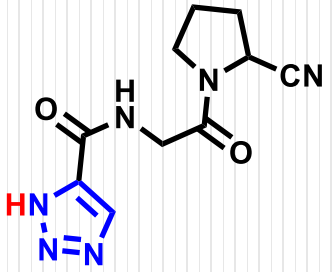
e) antifungal

J. Med. Chem. 1990, 33, 416



a) anti cancer

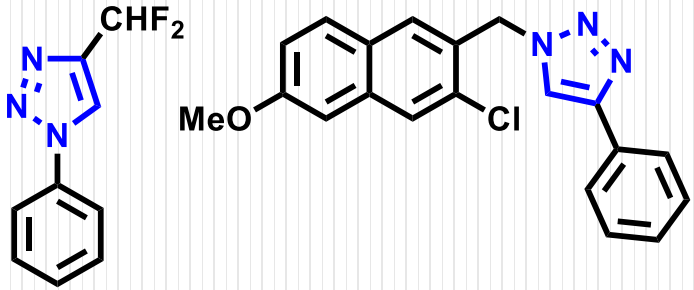
Bioorg. Med. Chem. Lett., 2014, 24, 2444



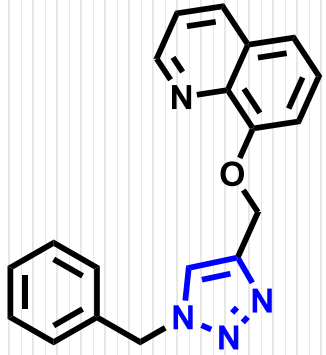
c) wound healer

Eur. J. Med. Chem., 2012, 51, 52

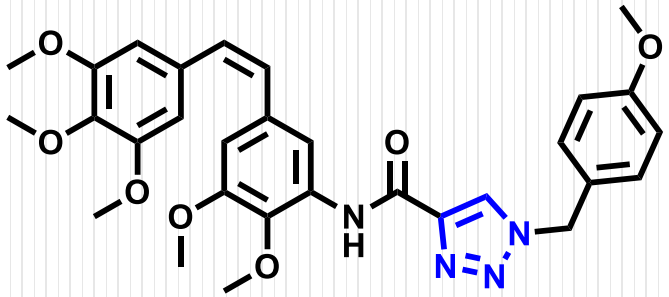
1,2,3-triazoles showing antimycotic activity



Chem. Asian J.
2011,*6,2696*

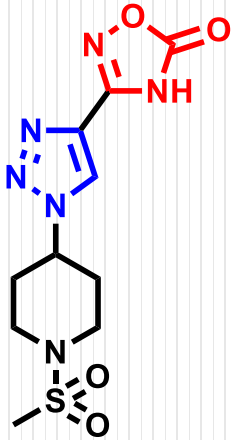


Eur. J. Med. Chem.,
2015,*93,246*

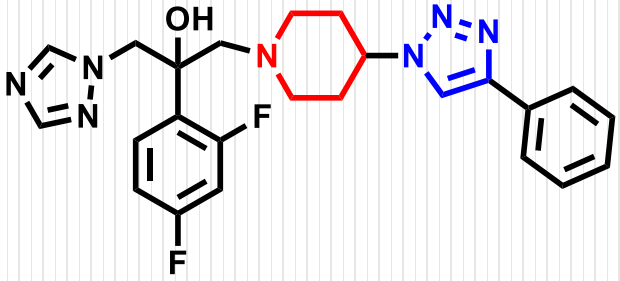


Bioorg. Med.Chem.,
2014,*22,5155*

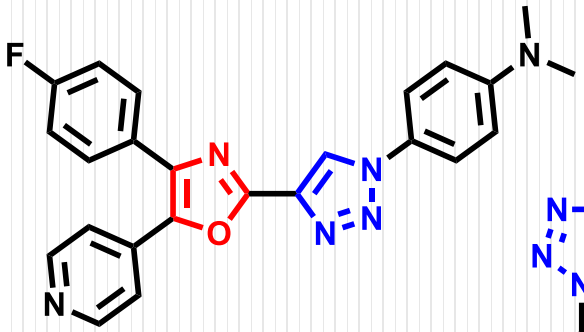
Hybrid 1,2,3-triazoles showing antimycotic activity



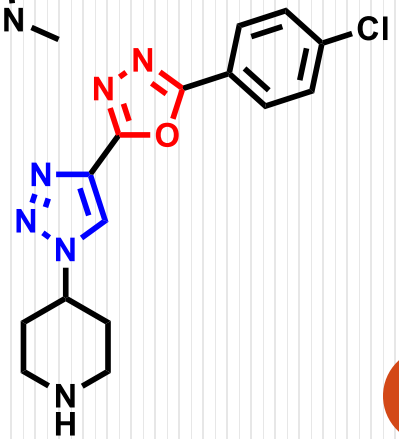
Bioorg. Med. Chem. Lett.
2009, *19,3564*



Eur. J. Med. Chem.
2014, *82, 490*

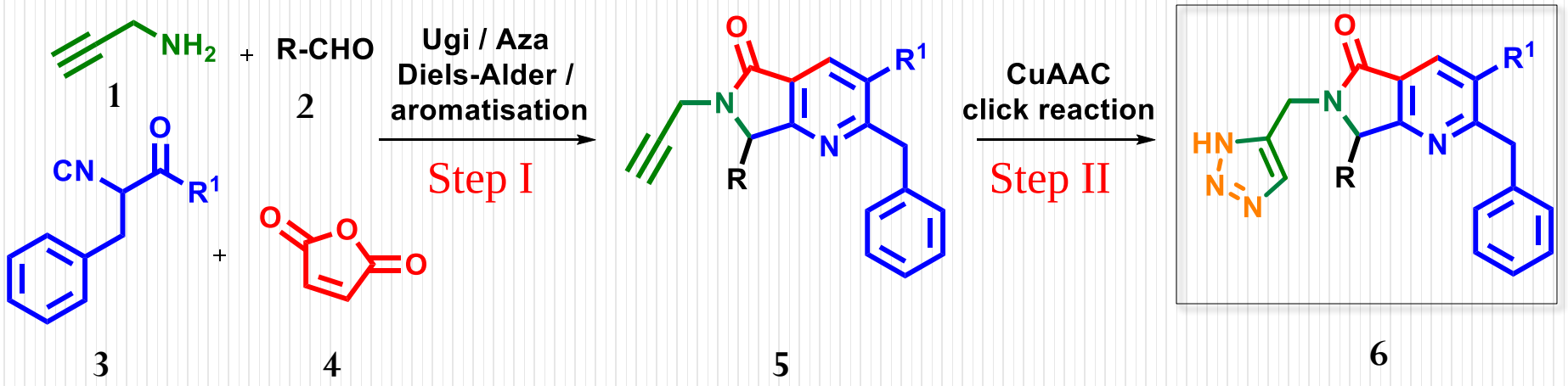


Bioorg. Med. Chem. Lett.
2014, *24,1352*



Bioorg. Med. Chem. Lett.
2011, *21, 444*

Proposed Methodology

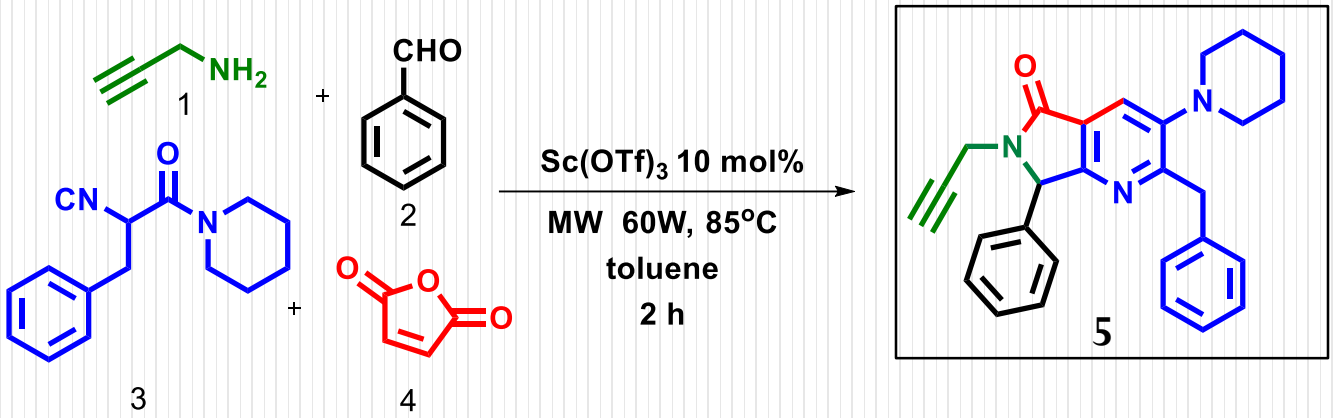


R = Ph, 4-NO_2Ph, 3,4-OMe-Phenethyl,
4-F-Ph, n-C_6H_{13}

R^1= morpholine, piperdine, diethyl amine

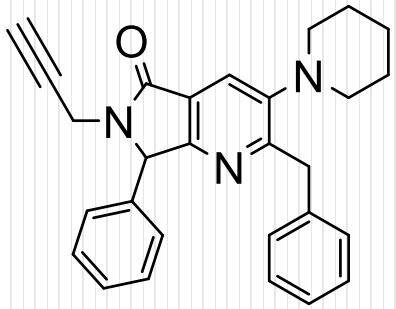
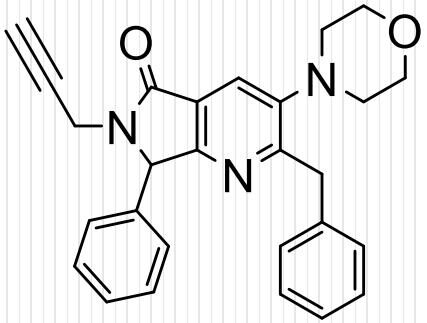
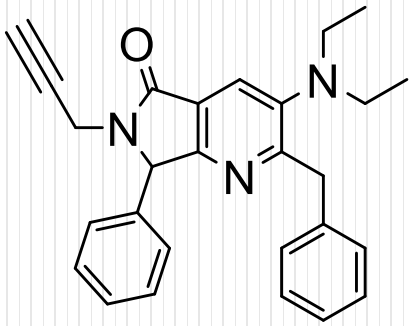
Conditions Optimization

Step I – Ugi / aza Diels-Alder / Aromatisation.

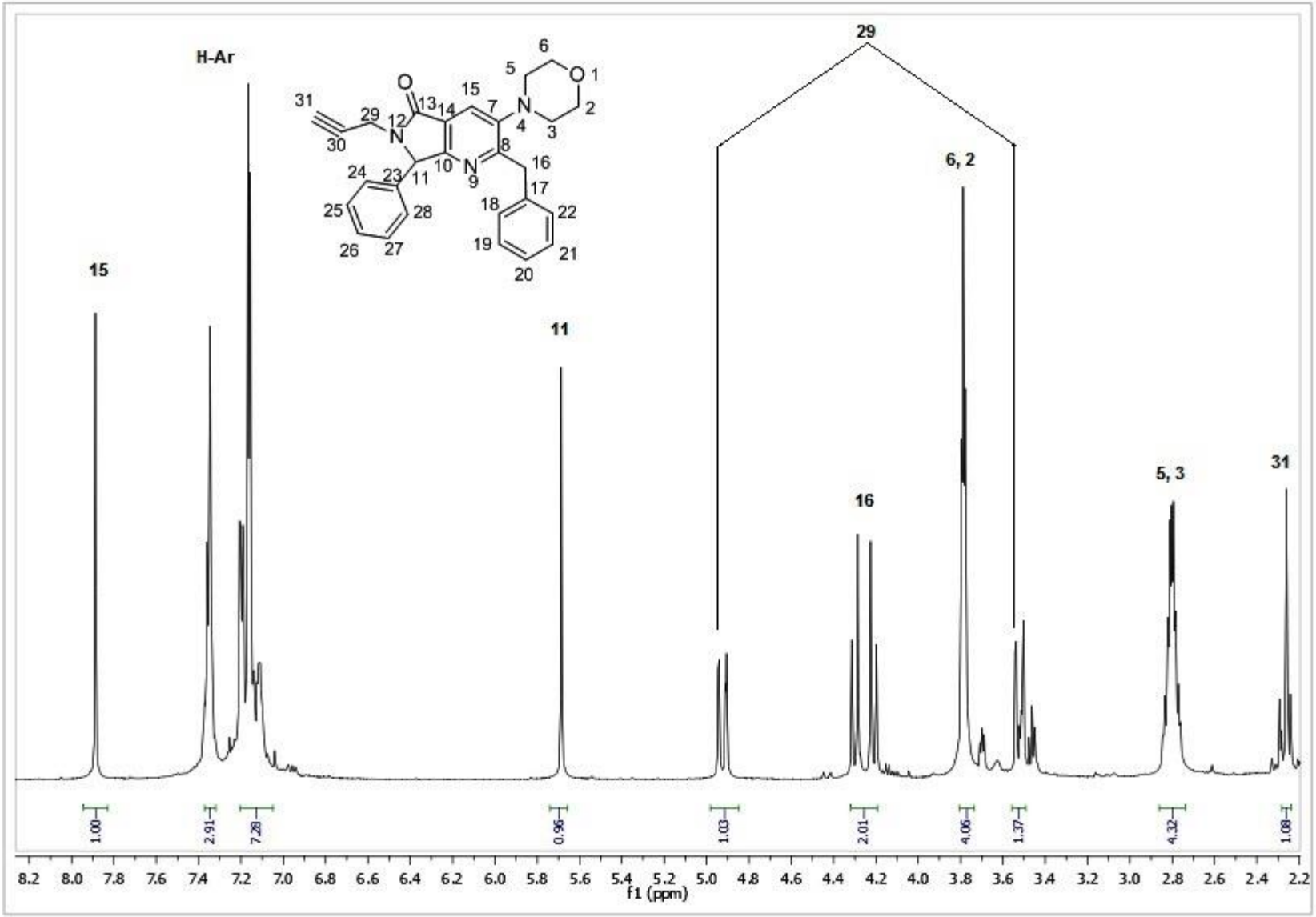


Sr. no.	Catalyst	Mol%	Temp(°C)/Time(h)	%Yield
1	-	-	RT / 24	NR
2	-	-	60 / 24	18
3	$InCl_3$	5	85 / 2 (MW)	22
4	$Sc(OTf)_3$	5	85 / 2 (MW)	43
5	$Sc(OTf)_3$	10	85 / 2 (MW)	69
6	$Sc(OTf)_3$	15	85 / 2 (MW)	67

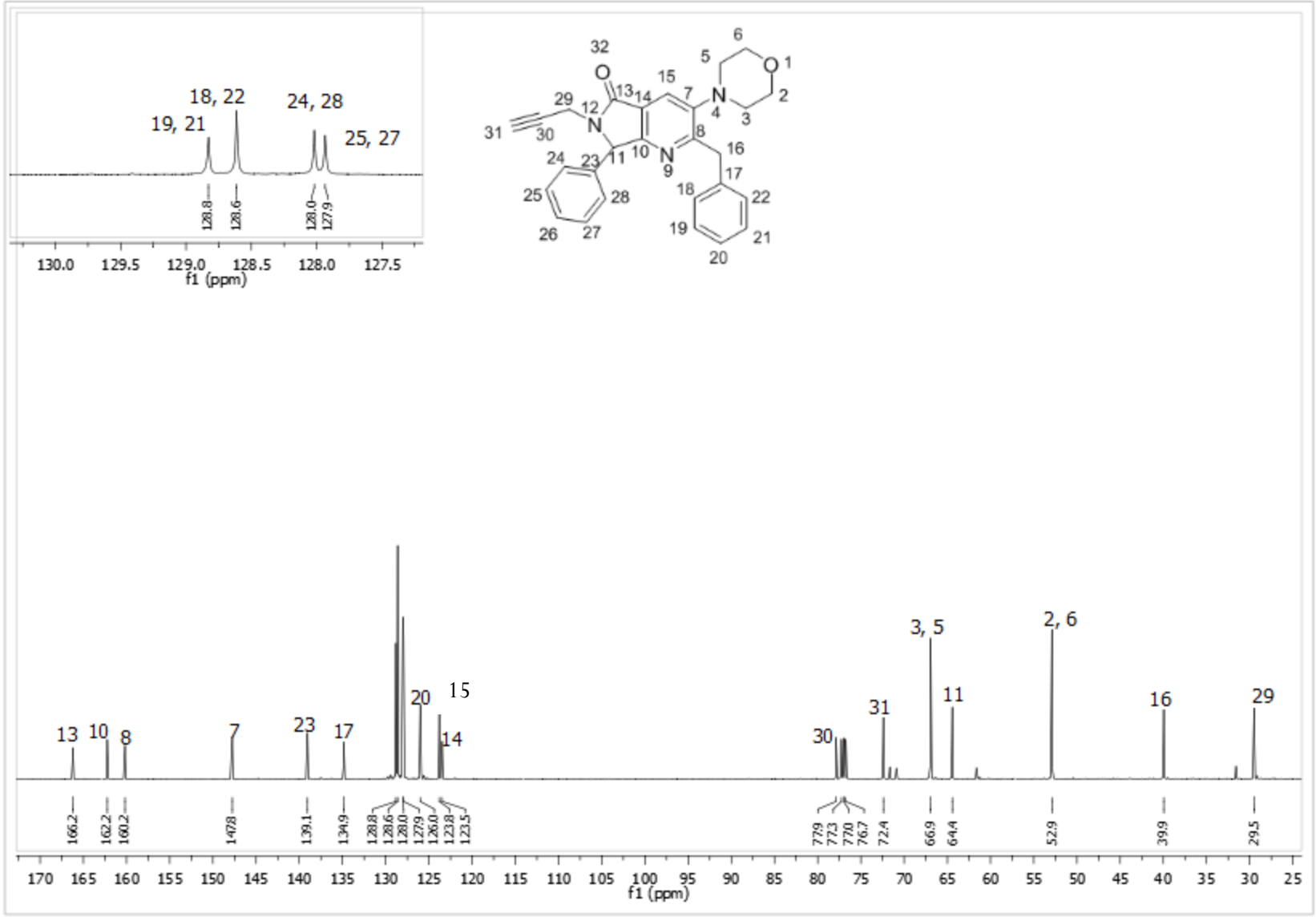
Results

Entry		%Yield
5a		69
5b		64
5c		58

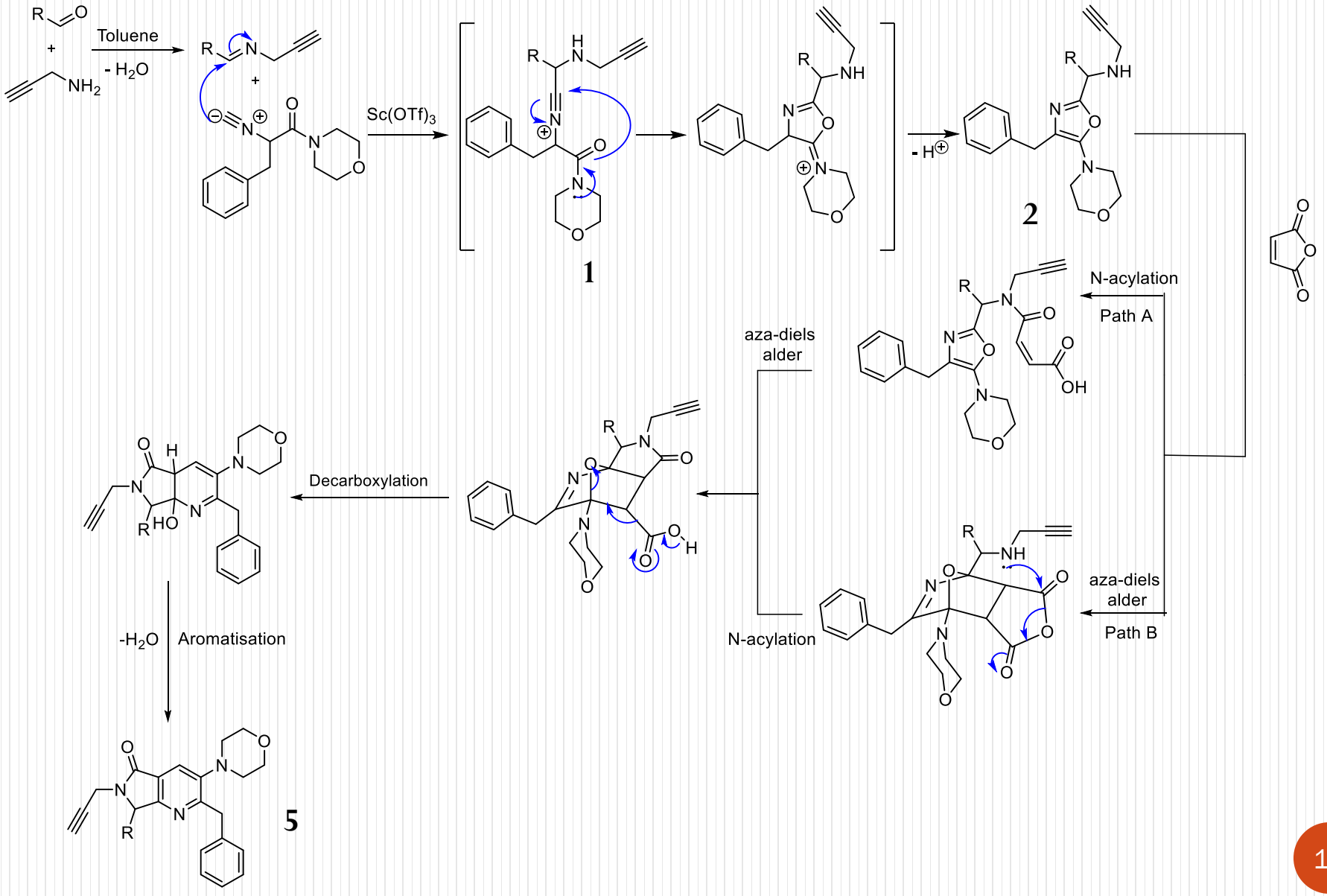
Proton NMR 5b



Carbon NMR 5b

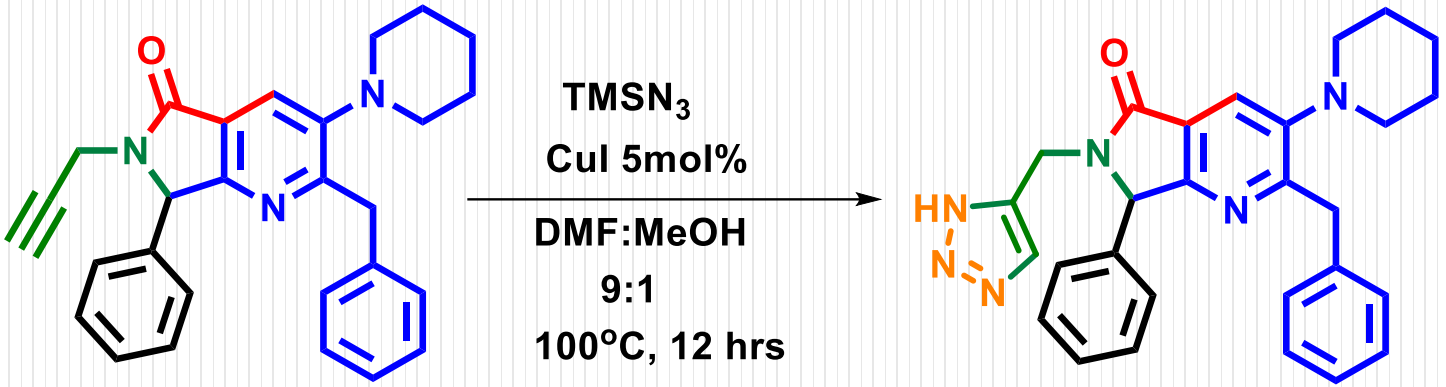


Reaction Mechanism



Conditions Optimization

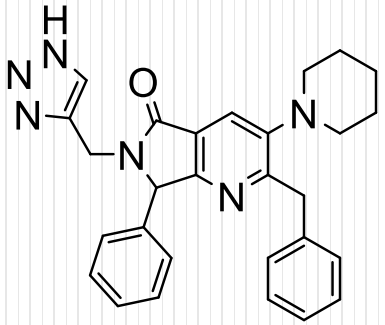
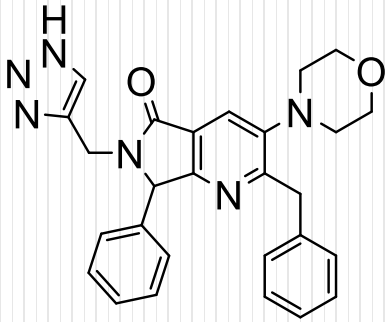
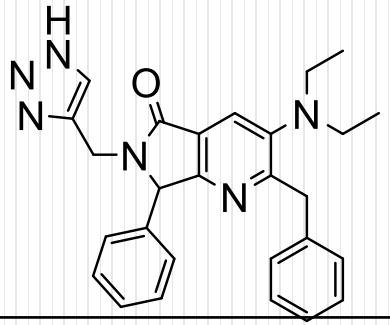
Step II – Azide-Alkyne cycloaddition



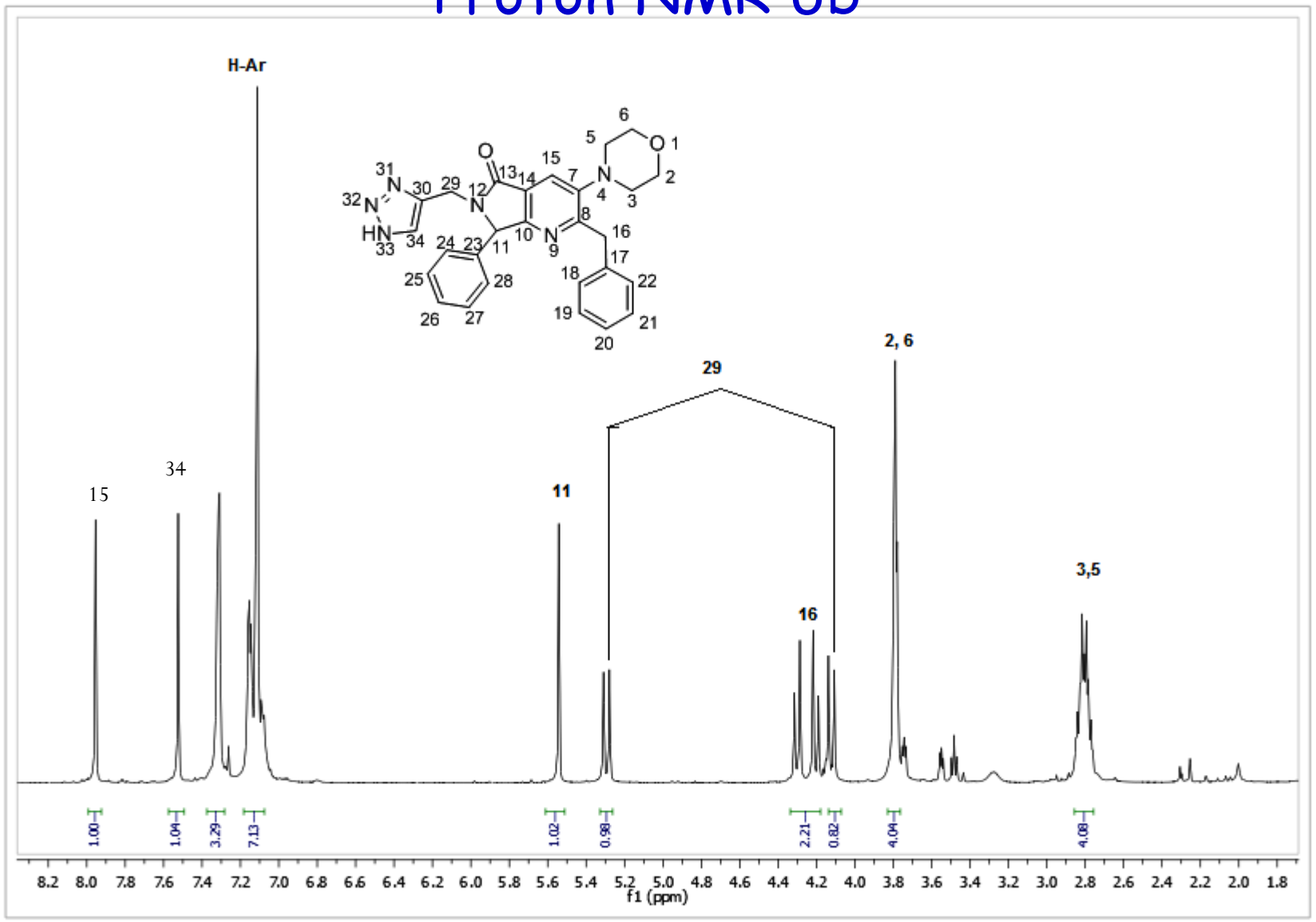
5 6

Sr. No.	CuI mol%	Time in hrs	%Yield
1.	5	12	73
2.	10	12	75
3.	5	16	68
4.	5	24	59

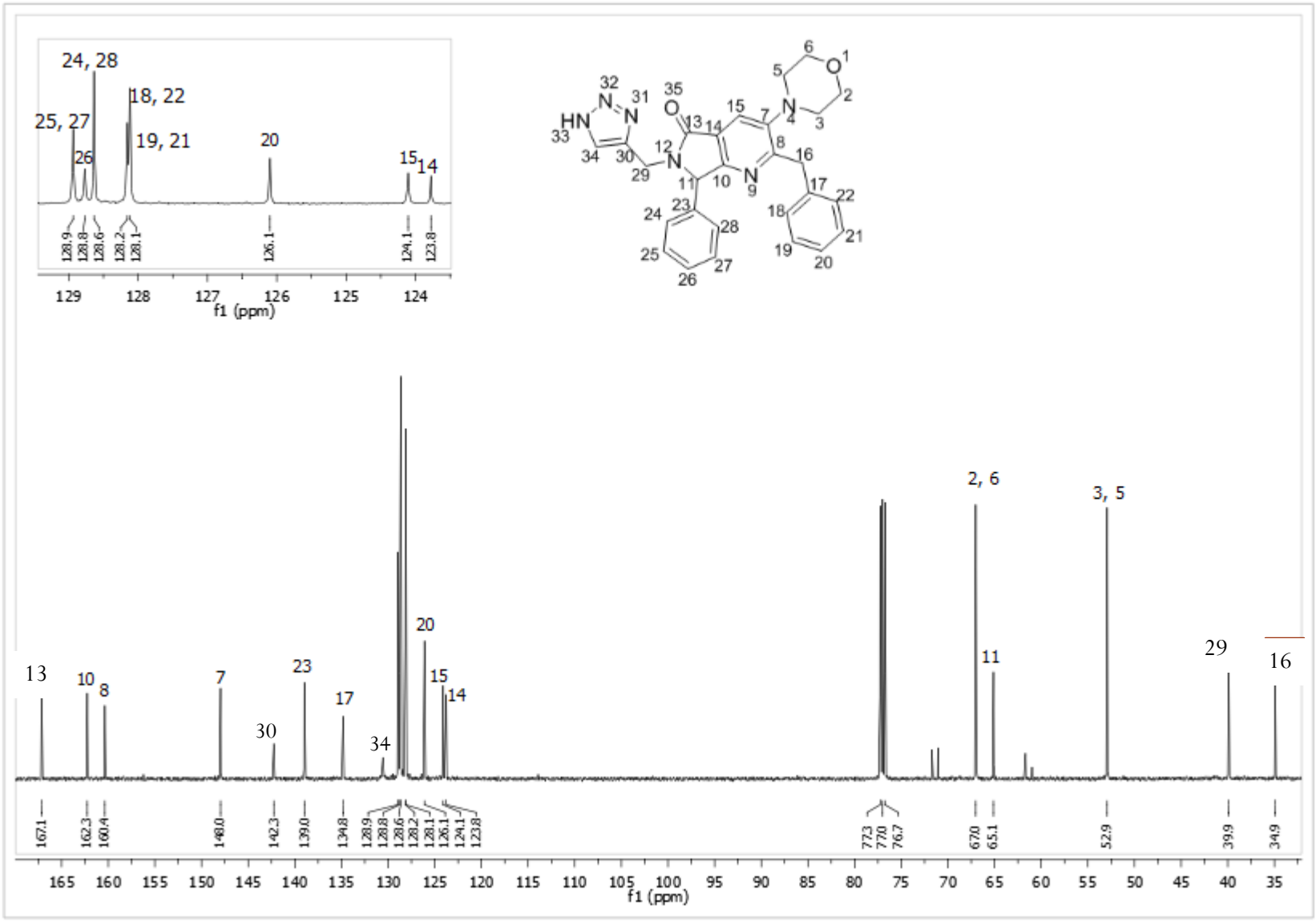
Results

Entry		%Yield
6a		73
6b		77
6c		72

Proton NMR 6b



Carbon NMR 6b



Conclusion

- We developed new method for the synthesis of pyrrolo[3,4-*b*]pyridine-5-ones (**5**) by three component Ugi, aza Diels-Alder cycloaddition, N-acylation, decarboxylation and aromatisation in one pot and 6-triazolylmethyl-pyrrolo[3,4-*b*]pyridine-5-ones (**6**) by azide-alkyne cycloaddition reaction in moderate to good yields by using MW-assisted reaction in two steps.